Where are we with Incretin Based Therapies for the Treatment of Diabetes?

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Denmark

Fundacion Fernandez-Cruz, Madrid October 2016
# GLP-1: Therapeutic Potential in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Type 2 diabetic phenotype</th>
<th>Actions of GLP-1</th>
</tr>
</thead>
</table>
| • Impaired β-cell function | • ↑ insulin secretion and biosynthesis  
• Improves β-cell function  
  (glucose sensitivity, proinsulin/insulin ratio)  
• Upregulates other genes essential for β-cell function  
  (eg. GLUT 2, glucokinase) |
| • Reduced β-cell mass | • ↑ β-cell proliferation/differentiation  
  animal studies  
• ↓ β-cell apoptosis  
  + human beta cells in vitro |
| • Glucagon hypersecretion | • ↓ glucagon secretion |
| • Overeating, obesity | • ↓ gastric emptying, ↑ satiety, ↓ appetite  
  → ↓ food intake & weight loss |
| • Macro- and microvascular complications | • Beneficial cardiovascular effects |
| • Insulin resistance | Actions which may be secondary to improved metabolic control  
• Improvements in insulin sensitivity |
GLP-1 based therapy of T2DM

• Based on the actions of GLP-1

• *GLP-1 agonists:* Short acting and long acting; *oral under development* (Phase III, very promising)

• *DPP-4 inhibitors:*  
  • Oral – daily or weekly  
  • prevent degradation of *both* GIP and GLP-1
DPP-4 inhibitors protect both GLP-1 and GIP and inhibit glucagon secretion in type 2 diabetes

Mari et al. J Clin Endocrinol Metab 2005
Sitagliptin + Metformin Factorial Study Design

N = 1091 Randomized
Mean baseline A1C = 8.8%

Screening Period
- Single-blind Placebo
  - Eligible if A1C 7.5 to 11%
  - Duration up to 12 weeks based on prior therapy

Diet/exercise Run-in Period
- Week-2
- Day 1
  - Open Label Cohort
    - Sitagliptin 50/Met 1000 BID

Double-blind Treatment Period
  - Placebo
  - Sitagliptin 100 mg qd
  - Metformin 500 BID
  - Metformin 1000 BID
  - Sitagliptin 50/Met 500 BID
  - Sitagliptin 50/Met 1000 BID
DPP-4 inhibition as combination therapy has sustained effects on HbA$_{1c}$

Sitagliptin (100 mg qd)
Metformin (500 mg bid)
Metformin (1000 mg bid)
Sitagliptin (50 mg bid) + metformin (500 mg bid)
Sitagliptin (50 mg bid) + metformin (1000 mg bid)

Data are for all patients treated cohort of the extension study

Williams-Herman D. Presented at: ADA 2008; EASD 2008
Acute Metformin and DPP-4 Inhibitor Co-Administration Increases Postprandial Intact GLP-1

### Day 2 of Administration

<table>
<thead>
<tr>
<th>Dose (Meal)</th>
<th>Intact GLP-1 (pmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td></td>
</tr>
</tbody>
</table>

#### Healthy subjects

- **Dose**: Placebo, Metformin (1000 mg), Sitagliptin (100 mg)
- **Meal**: Co-administration of sitagliptin (100 mg) + metformin (1000 mg)

#### T2DM subjects

- **Dose**: Placebo, Metformin (1000 mg)
- **Meal**: Co-administration of sitagliptin (100 mg) + metformin (1000 mg)
DPP-4 Inhibitor and Metformin Combination Reduces Postprandial Glucose Excursions Acutely in Drug Naïve Patients with T2DM

Day 2 of Administration

- **Sitagliptin (100 mg)**
- **Metformin (1000 mg)**
- **Placebo**
- **Co-administration of sitagliptin (100 mg) + metformin (1000 mg)**

Plasma Glucose (mg/dl)

-2 -1 0 1 2 4
(Dose) (Meal) Time (Hours)

Migoya et al. ADA 2010, Poster 572-P
Effect of metformin and GLP-1 antagonist on glucose and GLP-1 meal responses

12 patients with T2DM – mixed meal test

Hansen et al, JCEM 2016.
Effect of metformin and GLP-1 antagonist on glucose and GLP-1 meal responses

Hansen et al, JCEM 2016.
Effect of metformin and GLP-1 antagonist on glucose and GLP-1 meal responses

Hansen et al, JCEM 2016.
Effect of metformin and GLP-1 antagonist on glucose and GLP-1 meal responses

Data are mean values ± SEM

Hansen et al, JCEM 2016.
Why are DPP-4 inhibitors weight neutral:

Three reasons:

1. The simple
2. The complex
3. The important
Gastric emptying
Vomiting
Diarrhoea
Nausea
Abdominal pain
Appetite
Food intake
Weight loss
Glucagon secretion
Plasma glucose
Insulin secretion
Glucagon secretion
GLP-1 level during treatment with Incretin Mimetics
GLP-1 level during treatment with Incretin Enhancers
No.2

Only 10–15% of secreted GLP-1 reaches the pancreas intact, but GLP-1 action may involve the CNS.
No.3

Overview

PYY (1-36) and PYY (3-36)
Modulation of Appetite and Weight Loss

Hypothalamus

Appetite & Weight

NPY

PYY (1-36)

NPY (3-36)

Arcuate Nucleus

Blood - Brain Barrier

Inactivated GLP-1

DPP-IV

GLP-1

L Cell

GLP - 1

Deoxycholate
Oleate
N-Butyrate
Glucose
Amino Acids

Bowel Lumen

VIP

CCK
Effect of sitagliptin treatment on plasma PYY in T2DM at baseline, after 1 week and after 12 weeks

Aaboe et al DOM 2009
DPP-4 Inhibitors Appear to Have Good Tolerability

Pooled safety analyses

**Sitagliptin**: 25 large phase 2 and 3 clinical trials (up to 2 years duration)
- 7,726 patients exposed to sitagliptin (100 mg/d)
- 6,885 non-exposed patients
Engel et al; Diabetes Ther 2013

**Vildagliptin**: 38 large phase 2 and 3 clinical trials (up to 2 years duration)
- 6,116 patients exposed to vildagliptin (50 mg bid)
- 6,210 non-exposed patients
Schweizer et al; Vasc Health Risk Manag 2011

**Saxagliptin**: 20 phase 2 and 3 clinical trials (up to 4 years duration)
- 5,701 patients exposed to saxagliptin (2.5, 5 or 10 mg/d)
- 3,455 non-exposed patients
Hirshberg et al; Diabetes Metab Res Rev 2014

**Linagliptin**: 22 phase 3 clinical trials (up to 2 years duration)
- 4,810 patients exposed to linagliptin (5 mg/d)
- 2,590 non-exposed patients
Lehrke et al; Clin Ther 2014

Cardiovascular safety outcome trials

**Alogliptin**: EXAMINE (up to 40 months exposure; median 18 months)
- 2,701 patients exposed to alogliptin (6.25, 12.5 or 25 mg/d)
- 2,679 non-exposed patients
White et al; New Engl J Med 2013

**Saxagliptin**: SAVOR-TIMI (up to 2.9 years exposure; median 2.1 years)
- 8,280 patients exposed to saxagliptin (2.5 or 5 mg/d)
- 8,212 non-exposed patients
Scirica et al; New Engl J Med 2013

**Sitagliptin**: TECOS (up to 5.7 years exposure; median 3.0 years)
- 7,332 patients exposed to saxagliptin (100 or 50 mg/d)
- 7,339 non-exposed patients

DPP-4 inhibitors vs placebo or active comparator
No evidence for increased incidence of adverse events (including pancreatitis and malignancy)
Good tolerability in all patients (including the elderly, those with impaired renal function; those at high CV risk)
No evidence for any increase in cardiovascular risk
TECOS Study

- Large, pragmatic international trial designed to assess the impact of sitagliptin versus placebo on cardiovascular event rates
  - When added to usual diabetes care
  - Minimize difference in glycemia between groups
- Randomized, double-blind, placebo-controlled
- 14,671 patients with T2DM and established CVD: median F/up 3yrs
- Academically led in collaboration with industry sponsorship

The TECOS study – primary endpoint

Primary Composite Cardiovascular Outcome*
Per Protocol Analysis for Noninferiority

* CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina
Time to First Hospitalization for Heart Failure*

HR (95% CI): 1.00 (0.84–1.20)
P = 0.95

*ITT population

Frederiksberg Campus
Dias 36
SAVOR-TIMI 53, EXAMINE, and TECOS*: Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI</td>
<td>1.27 (1.07–1.51)</td>
<td>0.007</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>1.19 (0.89–1.59)</td>
<td>0.235</td>
</tr>
<tr>
<td>TECOS</td>
<td>1.00 (0.84–1.20)</td>
<td>1.000</td>
</tr>
<tr>
<td>SAVOR-TIMI + EXAMINE + TECOS</td>
<td>1.14 (0.97–1.34)</td>
<td>0.102</td>
</tr>
</tbody>
</table>

Test for heterogeneity for 3 trials: p=0.16, I²=44.9

* Unadjusted
GLP-1 analogues: structures and pharmacokinetics

Lixisenatide
Exenatide
Native GLP-1

Short acting

Semaglutide
Liraglutide

18-carbon fatty acid
16-carbon fatty acid

18-carbon fatty acid
16-carbon fatty acid

Long acting

DPP-4

Albiglutide
Dulaglutide

Exenatide-LAR

Meier JJ. Nat Rev Endocrinol 2012;8:728-742.
Semaglutide

94% homology to human GLP-1

$t_{1/2}$ of approximately 1 week, making it suitable for once-weekly dosing

Amino acid substitution at position 8
(alanine to alpha-aminoisobutyric acid) protects against DPP-4 degradation

Amino acid substitution at position 34
(lysine to arginine) prevents C-18 fatty di-acid binding at the wrong site

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; $t_{1/2}$, half-life; T2D, type 2 diabetes.

**Oral Semaglutide, principle**

- Semaglutide co-formulated with SNAC (Sodium N-[8-(2-hydroxybenzoyl) Amino] Caprylate (Eligen\textsuperscript{R}, Emisphere)
- Rapidly absorbed (min.) – daily dosing
- Bioavailability low and variable
- Plasma levels relatively constant because of long half-life of semaglutide
Oral Semaglutide, Phase II

• 600 patients with T2DM; baseline HbA1c = 7.9%; weight 92 kg
• 2.5 – 40 mg orally 26 weeks
• HbA1c: - 0.7 -> -1.9 %; placebo – 0.3%; semaglutide s.c. – 1.9 %
• Weight: plb. -1 kg; max oral and s.c. sema -6.5 kg;
• Side effects: gastrointestinal diminishing over time
**Consistent reductions in HbA$_{1c}$**

<table>
<thead>
<tr>
<th>SUSTAIN 1</th>
<th>SUSTAIN 2 vs. DPP-4 inhibitor</th>
<th>SUSTAIN 3 vs. QW GLP-1</th>
<th>SUSTAIN 4 vs. basal insulin</th>
<th>SUSTAIN 5 Add to basal insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>30 weeks</td>
<td>56 weeks</td>
<td>56 weeks</td>
<td>30 weeks</td>
</tr>
<tr>
<td>Baseline: 8.1%</td>
<td>Baseline: 8.1%</td>
<td>Baseline: 8.4%</td>
<td>Baseline: 8.2%</td>
<td>Baseline: 8.4%</td>
</tr>
<tr>
<td>Sema 0.5mg</td>
<td>Sema 0.5mg</td>
<td>Sema 1.0mg</td>
<td>Sema 0.5mg</td>
<td>Sema 0.5mg</td>
</tr>
<tr>
<td>1.0m</td>
<td>0.5mg</td>
<td>1.0m</td>
<td>1.0m</td>
<td>1.0mg</td>
</tr>
<tr>
<td>PBO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Change in HbA$_{1c}$ (%)

-1.5  
-1.6  
-1.3  
-1.5  
-1.2  
-1.6  
-1.5  
-1.9

*p<0.0001 vs. comparator

Impact of semaglutide on body weight

**SUSTAIN 1**
Monotherapy
30 weeks
Baseline: 92 kg

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sema 0.5 mg</td>
<td>-3.7 *</td>
</tr>
<tr>
<td>Sema 1.0 mg</td>
<td>-4.5</td>
</tr>
<tr>
<td>PBO</td>
<td>-1.0</td>
</tr>
</tbody>
</table>

**SUSTAIN 2 vs. DPP-4i**
56 weeks
Baseline: 89 kg

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sema 0.5 mg</td>
<td>-4.3 *</td>
</tr>
<tr>
<td>Sema 1.0 mg</td>
<td>-4.3</td>
</tr>
<tr>
<td>Sita 100 mg</td>
<td>-6.1</td>
</tr>
</tbody>
</table>

**SUSTAIN 3 vs. QW GLP-1**
56 weeks
Baseline: 96 kg

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sema 1.0 mg</td>
<td>-5.6 *</td>
</tr>
<tr>
<td>Exe 2.0 mg</td>
<td>-5.6 *</td>
</tr>
</tbody>
</table>

**SUSTAIN 4 vs. basal insulin**
30 weeks
Baseline: 93 kg

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sema 0.5 mg</td>
<td>-3.5 *</td>
</tr>
<tr>
<td>Sema 1.0 mg</td>
<td>-3.7 *</td>
</tr>
<tr>
<td>IGlar 29 U</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**SUSTAIN 5 Add to basal insulin**
30 weeks
Baseline: 92 kg

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sema 0.5 mg</td>
<td>-6.4 *</td>
</tr>
<tr>
<td>Sema 1.0 mg</td>
<td>-6.4 *</td>
</tr>
<tr>
<td>PBO</td>
<td>-1.4</td>
</tr>
</tbody>
</table>

* p<0.0001 vs. comparator
Subcutaneous delivery of exenatide by ITCA 650 (Intarcia) - Implantation interval 6 or 12 months

ITCA 650 60mcg vs Januvia® (sitagliptin) 100mg (Freedom 2) : -1.5% versus -0.8% (p < 0.001) 52 weeks; weight – 4 kg vs -1.3 kg (p < 0.001)
Adverse events: mild, gastrointestinal
J. Diab. Compl. 2014; 28: 393-
GLP-1: Beyond the pancreas

Liver
Glycogen storage

Brain
↓ Appetite
↓ Neuroprotection
↓ Neurogenesis

Heart
↑ Myocardial contractility
↑ Heart rate
↑ Myocardial glucose uptake
↓ Ischaemia-induced myocardial damage

Skeletal muscle
↑ Glucose uptake

Blood vessel
Endothelium-dependent vasodilation

Kidney
Natriuresis

Fat cells
↓ Glucose uptake
↓ Lipolysis

GI tract
Motility

Improvement in liver histology after 48 weeks of liraglutide treatment in patients with NASH

GLP-1: Beyond the pancreas

- **Brain**
  - Appetite
  - Neuroprotection
  - Neurogenesis

- **Heart**
  - Myocardial contractility
  - Heart rate
  - Myocardial glucose uptake
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- **Skeletal muscle**
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- **Blood vessel**
  - Endothelium-dependent vasodilation

- **Kidney**
  - Natriuresis

- **Fat cells**
  - Glucose uptake
  - Lipolysis

- **GI tract**
  - Motility

- **Liver**
  - Glycogen storage

Trial design – scale I – liraglutide for obesity

-500 kcal/day deficit diet + increased physical activity

Liraglutide 3.0 mg

Screening

Normoglycemia

Prediabetes

Placebo

Liraglutide 3.0 mg

Placebo

Liraglutide

Placebo

2-week follow-up

Week -2

Dose escalation

Main trial

12 week re-randomized period

Week 56

*Treated or untreated hypertension or dyslipidaemia according to ATP-III; Treatment ends at week 68 for individuals without prediabetes and is followed by an off-treatment follow-up period of 2 weeks. aRandomisation was stratified by prediabetes status at screening (ADA 2010 criteria) and baseline BMI (≥30 or <30 kg/m²)

Pi-Sunyer et al. NEJM 2015;373:11-22
Mean change in body weight
By prediabetes status: 0-56 weeks
Broadly similar results in 3-year prediabetic completers

Data are observed means with standard error bars, and the symbols at the right represent the 56-week weight change using LOCF imputation.

Pi-Sunyer et al. NEJM 2015;373:11-22
Liraglutide is not approved for weight management outside Canada, EU and US

**Time of onset of type 2 diabetes**

Baseline to week 56
at 3 years broadly similar results – an 80% risk reduction

![Graph showing time of onset of type 2 diabetes](image)

**Figure** shows the proportion of patients who received a diagnosis of type 2 diabetes during the course of the 56-week main trial period. Findings from logistic regression analysis showed an odds ratio for development of diabetes of 8.1 (95% CI, 2.6 to 25.3). All patients in whom diabetes had developed had prediabetes at screening, except for one patient in the placebo group (indicated by a red circle), who had normoglycemia. The numbers along the graphs show the cumulative number of patients who received a diagnosis of diabetes over the course of 56 weeks. The numbers of patients at risk (i.e., remaining in the trial) are shown in the table beneath the x axis.

**Table: Cumulative No. of Patients Receiving a Diagnosis of Diabetes over 56 Weeks (No. at Risk)**

<table>
<thead>
<tr>
<th>Week</th>
<th>Liraglutide 3.0 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2219</td>
<td>1225</td>
</tr>
<tr>
<td>2</td>
<td>2210</td>
<td>1210</td>
</tr>
<tr>
<td>3</td>
<td>2137</td>
<td>1204</td>
</tr>
<tr>
<td>4</td>
<td>2130</td>
<td>1096</td>
</tr>
<tr>
<td>5</td>
<td>2130</td>
<td>1035</td>
</tr>
<tr>
<td>8</td>
<td>984</td>
<td>911</td>
</tr>
<tr>
<td>10</td>
<td>908</td>
<td>818</td>
</tr>
<tr>
<td>11</td>
<td>908</td>
<td>817</td>
</tr>
<tr>
<td>12</td>
<td>908</td>
<td>816</td>
</tr>
<tr>
<td>13</td>
<td>908</td>
<td>813</td>
</tr>
</tbody>
</table>

P<0.001

Pi-Sunyer et al. *NEJM* 2015;373:11-22
GLP-1: Beyond the pancreas

- Brain:
  - Appetite
  - Neuroprotection
  - Neurogenesis

- Heart:
  - Myocardial contractility
  - Heart rate
  - Myocardial glucose uptake
  - Ischaemia-induced myocardial damage

- GI tract:
  - Motility

- Liver:
  - Glycogen storage

- Fat cells:
  - Glucose uptake
  - Lipolysis

- Kidney:
  - Natriuresis

- Skeletal muscle:
  - Glucose uptake

- Blood vessel:
  - Endothelium-dependent vasodilation

Cardiovascular effects of GLP-1: four distinct mechanisms

• Improves myocardial performance in non-ischaemic heart failure

• Improves myocardial survival in ischaemic heart disease

• Improves endothelial dysfunction in T2DM

• Decreases cardiovascular risk markers in T2DM
The TECOS study – primary endpoint

Primary Composite Cardiovascular Outcome*  
Per Protocol Analysis for Noninferiority

HR (95% CI): 0.98 (0.88, 1.09)  
Noninferiority P <0.001

*CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina
ELIXA

- Elixa randomized 6068 patients with T2DM post coronary syndrome to lixisenatide or placebo (+ other medications) for just over 2 years.

- Primary outcome (CV death, MI, stroke, hospitalization for unstable angina) 13.4% vs 13.2 %, HR 1.02

- Primary outcome + HF hosp. + coron. revasc. 21.8% vs 21.7%, HR 1.00 (0.9-1.11)

- No increase in pancreatitis or pancreatic cancer or any cancer

Treatment of Type 2 Diabetes with GLP-1 receptor agonists

LEADER: Study design

Key inclusion criteria
- T2DM, HbA1c ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/predmix insulin
- Age ≥50 years and established CV disease or chronic renal failure
  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria
- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

CV: cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; HbA1c: glycated hemoglobin; MEN-2: multiple endocrine neoplasia type 2; MTC: medullary thyroid cancer; OAD: oral antidiabetic drug; OD: once daily; T2DM: type 2 diabetes mellitus.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.
Primary outcome
CV death, non-fatal myocardial infarction, or non-fatal stroke

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.

CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

EMP-A-Reg (Zinman et al NEJM sept 2015)

Liraglutide is not approved for weight management.

7000 patients with severe established cardiovascular disease studied for 3 years.
Empagliflozin and Liraglutide

**EMPA-REG OUTCOME**
CV death, non-fatal MI, or non-fatal

- **Placebo**
  - Patients with an event (%): 8, 10, 12, 14, 16, 18, 20

- **Empagliflozin**
  - Patients with an event (%): 7, 9, 11, 13, 15, 17, 19

  **HR: 0.86**
  **95.02% CI (0.74 – 0.99)**
  **p=0.04**

**Patients at risk**
- **Empagliflozin**: 4887, 4580, 4455, 4328, 3851, 2821, 2359, 1534, 370
- **Placebo**: 2333, 2256, 2194, 2112, 1875, 1380, 1161, 741, 166

**LEADER**
CV death, non-fatal MI, or non-fatal stroke

- **Placebo**
  - Patients with an event (%): 6, 8, 10, 12, 14, 16, 18

- **Liraglutide**
  - Patients with an event (%): 5, 7, 9, 11, 13, 15, 17

  **HR: 0.87**
  **95% CI (0.78 – 0.97)**
  **p=0.01**

**Patients at risk**
- **Liraglutide**: 4668, 4593, 4496, 4400, 4280, 4172, 4072, 3982, 1562, 424
- **Placebo**: 4672, 4588, 4473, 4352, 4237, 4123, 4010, 3914, 1543, 407

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24, June 13 2016, New Orleans, LA, USA.
### Individual components of the primary endpoint

#### EMPA-REG OUTCOME

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
<th>p-value</th>
<th>Empa</th>
<th>Pbo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>0.86 (0.74–0.99)*</td>
<td>0.04</td>
<td>490/4687</td>
<td>282/2333</td>
</tr>
<tr>
<td>CV death</td>
<td>0.62 (0.49–0.77) &lt;0.0001</td>
<td>172/4687</td>
<td>137/2333</td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.87 (0.70–1.09)</td>
<td>0.22</td>
<td>213/4687</td>
<td>121/2333</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1.24 (0.92–1.67)</td>
<td>0.16</td>
<td>150/4687</td>
<td>60/2333</td>
</tr>
</tbody>
</table>

#### LEADER

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
<th>p-value</th>
<th>Lira</th>
<th>Pbo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>0.87 (0.78–0.97)</td>
<td>0.01</td>
<td>608/4668</td>
<td>694/4672</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.66–0.93)</td>
<td>0.007</td>
<td>219/4668</td>
<td>278/4672</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.88 (0.75–1.03)</td>
<td>0.11</td>
<td>281/4668</td>
<td>317/4672</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>0.89 (0.72–1.11)</td>
<td>0.30</td>
<td>159/4668</td>
<td>177/4672</td>
</tr>
</tbody>
</table>

*95.02% CI.

CV: cardiovascular; Empa: empaglifloin; Lira: liraglutide; MACE: major adverse cardiovascular event; MI: myocardial infarction; Pbo: placebo.

### Empa-Reg; lab data

#### Section S. Clinical laboratory data.

Table S14. Changes in clinical laboratory parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change from baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>41.1 ± 5.7</td>
<td>0.9 ± 4.7</td>
<td>41.2 ± 5.6</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.4 ± 1.5</td>
<td>-0.1 ± 1.2</td>
<td>13.4 ± 1.5</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.03 ± 0.29</td>
<td>0.03 ± 0.22</td>
<td>1.02 ± 0.28</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min/1.73m²</td>
<td>74.0 ± 21.1</td>
<td>-2.0 ± 11.5</td>
<td>74.4 ± 21.8</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>14 ± 12</td>
<td>0 ± 24</td>
<td>13 ± 10</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>18 ± 14</td>
<td>0 ± 32</td>
<td>17 ± 11</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>64 ±32</td>
<td>5 ± 33</td>
<td>65 ± 32</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>141 ± 2</td>
<td>0 ± 2</td>
<td>141 ± 2</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>4.3 ± 0.4</td>
<td>0.0 ± 0.4</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>9.7 ± 0.5</td>
<td>0.0 ± 0.5</td>
<td>9.7 ± 0.4</td>
</tr>
<tr>
<td>Magnesium, mEq/L</td>
<td>1.7 ±0.2</td>
<td>0.0 ± 0.2</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>Chloride, mEq/L</td>
<td>102 ± 2</td>
<td>-1 ± 2</td>
<td>102 ± 2</td>
</tr>
<tr>
<td>Phosphate, mg/dL</td>
<td>3.7 ± 0.3</td>
<td>0.0 ± 0.3</td>
<td>3.7 ± 0.3</td>
</tr>
</tbody>
</table>

What about HbA$_{1c}$?

![Graph showing HbA$_{1c}$ levels over time and the estimated treatment difference (ETD) at month 36.]

ETD at month 36: -0.40%

95% CI (-0.45; -0.34)

Number of patients at each visit

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>4668</td>
<td>4672</td>
</tr>
<tr>
<td>6 months</td>
<td>4402</td>
<td>4413</td>
</tr>
<tr>
<td>12 months</td>
<td>4355</td>
<td>4355</td>
</tr>
<tr>
<td>18 months</td>
<td>4335</td>
<td>4335</td>
</tr>
<tr>
<td>24 months</td>
<td>4307</td>
<td>4307</td>
</tr>
<tr>
<td>30 months</td>
<td>4279</td>
<td>4279</td>
</tr>
<tr>
<td>36 months</td>
<td>4251</td>
<td>4251</td>
</tr>
<tr>
<td>48 months</td>
<td>4223</td>
<td>4223</td>
</tr>
<tr>
<td>54 months</td>
<td>4205</td>
<td>4205</td>
</tr>
<tr>
<td>End of trial</td>
<td>4177</td>
<td></td>
</tr>
</tbody>
</table>

Data are estimated mean values from randomisation to EOT.

CI, confidence interval; EOT, end of trial; ETD, estimated treatment difference; HbA$_{1c}$, glycosylated haemoglobin.

What about body weight in LEADER?

ETD at month 36: -2.3 kg
95% CI (-2.5 ; -2.0)

Number of patients at each visit

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 months</td>
<td>4667</td>
<td>4671</td>
</tr>
<tr>
<td>36 months</td>
<td>4434</td>
<td>4423</td>
</tr>
<tr>
<td>36 months</td>
<td>4324</td>
<td>4285</td>
</tr>
<tr>
<td>48 months</td>
<td>4088</td>
<td>3970</td>
</tr>
<tr>
<td>48 months</td>
<td>3835</td>
<td>3680</td>
</tr>
<tr>
<td>48 months</td>
<td>824</td>
<td>766</td>
</tr>
<tr>
<td>EOT</td>
<td>3708</td>
<td>3555</td>
</tr>
</tbody>
</table>

Data are estimated mean values from randomisation to EOT.
CI, confidence interval; EOT, end of trial; ETD, estimated treatment difference.
Antihyperglycaemic medications introduced during trial

- Metformin
- Sulphonylureas
- Alpha-glucosidase inhibitors
- TZDs
- Glinides
- Insulin

### Additional classes added

<table>
<thead>
<tr>
<th>Class</th>
<th>Liraglutide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1RAs</td>
<td>149</td>
<td>170</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>100</td>
<td>130</td>
</tr>
</tbody>
</table>

DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2, sodium-glucose co-transporter-2; TZD, thiazolidinedione.

SUSTAIN 6 Trial design

**Randomisation (1:1:1:1)**

- **3297 subjects with T2D**
  - Age ≥50 years with clinical evidence of CVD or ≥60 years with subclinical evidence of CVD
  - Previously on 0–2 OADs, basal or premix insulin ± 0–2 OADs
  - HbA1c ≥7.0%

- **Semaglutide 1.0 mg**
- **Semaglutide 0.5 mg**
- **Placebo 1.0 mg**
- **Placebo 0.5 mg**

**Trial Information**

- Trial product was given in addition to standard of care and investigators were encouraged to treat according to local guidelines to achieve optimal glycemic control
- Subjects were randomised to semaglutide or volume-matched placebo and stratified according to CVD status, insulin treatment and eGFR
- Included a planned observation period of 109 weeks for all subjects (a 104-week treatment period with a 5-week follow-up period), with at least 122 events of the primary outcome
- Dose escalation from a starting dose of 0.25 mg, dose doubled every 4 weeks until trial dose achieved

**Treatment duration 104 weeks**

- Dose escalation 4–8 weeks
- Maintenance treatment 96–100 weeks
- Follow-up 5 weeks
Cardiovascular Outcomes.

A Primary Outcome

Hazard ratio, 0.74 (95% CI, 0.58–0.95)
P=0.001 for noninferiority
P=0.02 for superiority

B Nonfatal Myocardial Infarction

Hazard ratio, 0.74 (95% CI, 0.51–1.08)
P=0.12

No. at Risk
Placebo 1649 1618 1586 1567 1534 1508 1479
Semaglutide 1648 1619 1601 1584 1568 1543 1524

C Nonfatal Stroke

Hazard ratio, 0.61 (95% CI, 0.38–0.99)
P=0.04

No. at Risk
Placebo 1649 1629 1611 1597 1571 1548 1528
Semaglutide 1648 1633 1619 1606 1593 1572 1558

D Death from Cardiovascular Causes

Hazard ratio, 0.98 (95% CI, 0.65–1.48)
P=0.92

No. at Risk
Placebo 1649 1637 1623 1617 1600 1584 1566
Semaglutide 1648 1634 1627 1617 1607 1589 1579

Glycated Hemoglobin and Body Weight.

**A** Glycated Hemoglobin

- Placebo, 1.0 mg
- Placebo, 0.5 mg
- Semaglutide, 0.5 mg
- Semaglutide, 1.0 mg

**B** Body Weight

- Placebo, 1.0 mg
- Placebo, 0.5 mg
- Semaglutide, 0.5 mg
- Semaglutide, 1.0 mg

Change in blood pressure

ESTIMATED TREATMENT DIFFERENCES AT WEEK 104

**Systolic BP (mmHg)**
Baseline: 135.6 mmHg

**Diastolic BP (mmHg)**
Baseline: 77.0 mmHg

- **Semaglutide 0.5 mg**
  - **ETD [95% CI]**: -1.27 [-2.77; 0.23]
  - **ETD (semaglutide – placebo)**

- **Semaglutide 1.0 mg**
  - **ETD [95% CI]**: -2.5* [-4.09; -1.08]

- **ETD (semaglutide – placebo)**

*Indicates significance (p-value < 0.001). Values are ETD with 95% CIs from a mixed model for repeated measurements analysis using ‘in-trial’ data from subjects in the full analysis set.

BP, blood pressure; ETD, estimated treatment difference; CI, confidence interval.
Revascularisation
CORONARY AND PERIPHERAL

Kaplan Meier plot for time from randomisation to first revascularisation using ‘in-trial’ data from subjects in the full analysis set. HR is from a stratified proportional hazard model. Peripheral events were not EAC confirmed.
CI, confidence interval; EAC, (external) event adjudication committee; HR, hazard ratio.

HR, 0.65 (95% CI, 0.50–0.86)
Events: 83 semaglutide; 126 placebo
p=0.003
Summary of cardiovascular outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>0.74* [0.58;0.95]</td>
</tr>
<tr>
<td>CV death</td>
<td>0.98 [0.65;1.48]</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.74 [0.51;1.08]</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>0.61* [0.38;0.99]</td>
</tr>
<tr>
<td>All-cause death, non-fatal MI or non-fatal stroke</td>
<td>0.77* [0.61;0.97]</td>
</tr>
<tr>
<td>All-cause death</td>
<td>1.05 [0.74;1.50]</td>
</tr>
<tr>
<td>Expanded CV outcome</td>
<td>0.74* [0.62;0.89]</td>
</tr>
<tr>
<td>Unstable angina requiring hospitalisation</td>
<td>0.82 [0.47;1.44]</td>
</tr>
<tr>
<td>Hospitalisation for heart failure</td>
<td>1.11 [0.77;1.61]</td>
</tr>
<tr>
<td>Revascularisation</td>
<td>0.65* [0.50;0.86]</td>
</tr>
</tbody>
</table>

*Indicates significance (p-value <0.05). Values are estimated HRs with 95% CIs from a Cox proportional hazards model using 'in-trial' data from subjects in the full analysis set. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
New or worsening nephropathy

HR, 0.64 (95% CI, 0.46–0.88)
Events: 52 semaglutide; 100 placebo
p=0.005

Kaplan-Meier plot for time from randomisation to first PRO-confirmed new or worsening nephropathy using in-trial data from subjects in the full analysis set. HRs from a proportional hazard model.

CI, confidence interval; PRO, (proportional) event adjudication committee; HR, hazard ratio.
conclusions

• The DPP-4 inhibitors are safe and particularly effective with metformin. GLP-1 may be involved in metformin actions.

• Some of the newer GLP-1 agonists may be more effective, and oral and sustained release preparations are on their way.

• First GLP-1 agonist approved for weight loss, shows promise for diabetes prevention.

• Long term trials in 12000 high risk individuals (LEADER + SUSTAIN) show significantly reduced cardiovascular risk, perhaps because of anti-atherogenic actions.